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<p>(54) Title: QUINOLINE DERIVATIVES AS ANTAGONISTS OF LEUKOTRIENE D₄</p> <p>(57) Abstract</p> <p>This invention relates to certain quinoline-diaryl compounds and their use as leukotriene D₄ antagonists for the treatment of hypersensitive disorders.</p>		

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QUINOLINE DERIVATIVES AS ANTAGONISTS
OF LEUKOTRIENE D₄

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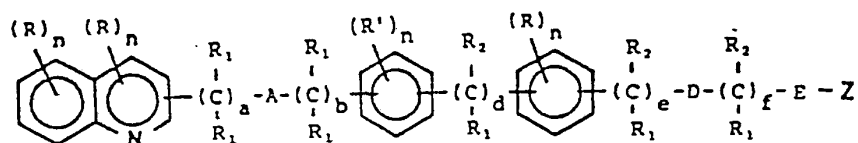
Field of Invention

This invention relates to quinolinyl phenylalkyl compounds
and their use as valuable pharmaceutical agents, particularly
as lipxygenase inhibitors and/or leukotriene antagonists
10 possessing anti-inflammatory and anti-allergic properties.

Summary of the Invention

15

This invention relates to the compounds described by the
general Formula I and to therapeutic compositions comprising
as active ingredient a compound of Formula I:



5

Formula I

where:

A is O or S;

10 D is O, S, NR₁, $\overset{R_1}{\underset{R_1}{-C}} = \overset{R_2}{\underset{R_2}{C}} -$ or a chemical bond

E is a chemical bond or $\overset{R_1}{\underset{R_1}{-C}} = \overset{R_2}{\underset{R_2}{C}} -$;

a is 0-2;

b is 0-1;

15 d is 1-5;

e is 0-4;

f is 0-5;

n is 0-2;

20 R is independently hydrogen, alkyl, hydroxy, alkoxy, carboxy, carbalkoxy, halo, nitro, haloalkyl, cyano or acyl;

R' is independently hydrogen, alkyl, hydroxy, alkoxy, halo or haloalkyl;

R₁ is independently hydrogen, alkyl or aralkyl;

R₂ is $-(CH_2)_x - X$;

25 x is 0-3;

X is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, mono- and di-alkylamino, aralkylamino, acylamino, carbamyl, carboxy, carbalkoxy, tetrazolyl or acylsulfonamido;

30 vicinal R₂ groups together may be $-(CH_2)_y-$, where y is 1-4, thus forming a 3-6 membered ring;

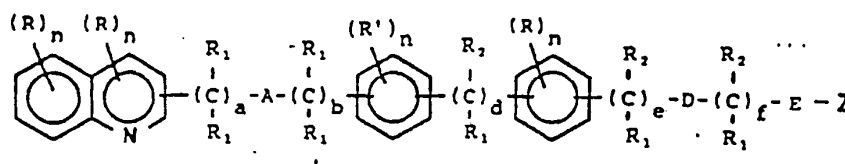
geminal R₁ and R₂ groups may together form a spiro substituent, $-(CH_2)_z-$, where z is 2 to 5;

geminal R_1 or R_1 and R_2 groups may together form an alkylidenyl substituent, $=CHR_1$;

Z is $-COOR_1$, CN , $-CNHSO_2R_1$, $-CN(R_1)_2$, $-OR_1$, tetrazolyl or substituted tetrazolyl where the substituent may be alkyl, carboxyalkyl or carbalkoxyalkyl;

R_1 is hydrogen, alkyl, haloalkyl, phenyl or benzyl; and pharmaceutically acceptable salts thereof.

10 The compounds of Formula I contain at least three aromatic rings. For the purposes of this invention these may be designated as shown in Formula II. The substitution pattern of these rings along the chain with respect to each other is as follows.

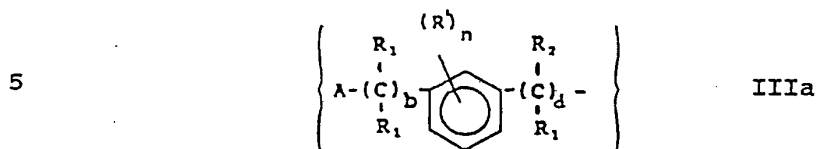


15 Ring I Ring II Ring III

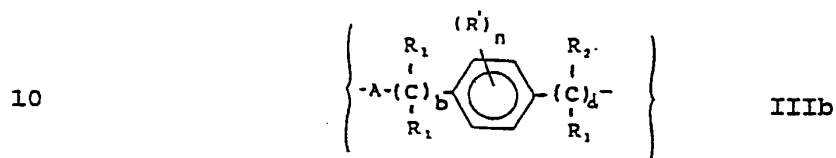
Formula II

20 The substitution pattern of the quinoline ring, that is Ring I, is preferably at the 2-position for extending the side chain. As this side chain progresses from the quinoline ring, the two phenyl rings, designated Ring II and Ring III may be substituted along the chain in the ortho, meta or para positions with respect to each other and Ring II may also be substituted in the ortho, meta and para positions in respect to the quinoline ring.

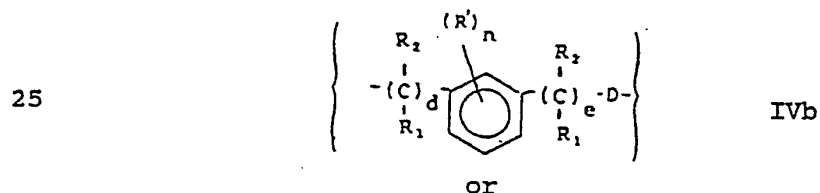
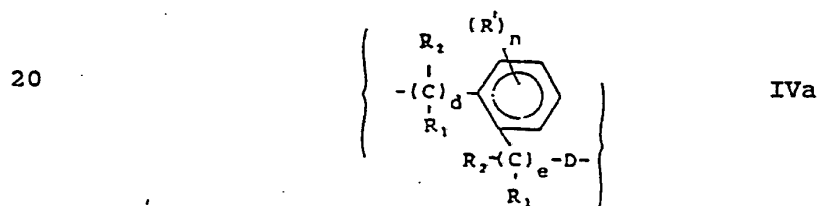
The preferred substitution pattern for Ring II is meta or para, that is:



or

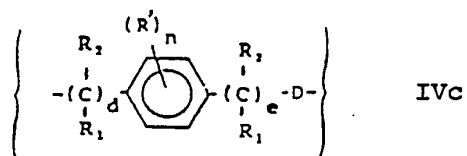


Ring III however may be substituted equally in the ortho,
15 meta or para positions, that is:

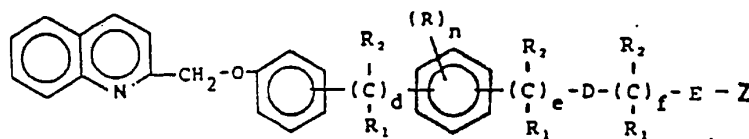


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10 Further preferred compounds of this invention are described by Formula V below:



15

Formula V

where

R, R, R, d, e, f, n, D, E and Z are as described above.

The more preferred compounds of Formula V are those where

20

Z is $-\text{COOR}_1$; $-\text{CN}$; $-\text{C}(=\text{O})\text{NH}\text{SO}_2\text{R}_1$ or tetrazolyl.

In addition, the present invention relates to the method of using these compounds as lipooxygenase inhibitors and/or leukotriene antagonists possessing anti-inflammatory and anti-allergic properties.

- 5 As employed above and throughout the disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

10 "Alkyl", either alone or with various substituents defined herein, means a saturated aliphatic hydrocarbon, either branched or straight chained. A "loweralkyl" is preferred having about 1 to about 6 carbon atoms. Examples of alkyl include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, t-butyl, amyl, hexyl, etc.

15 "Alkoxy" refers to a loweralkyl-O-group.

"Alkenyl" refers to a hydrocarbon having at least one point of unsaturation and may be branched or straight chained. Preferred alkenyl groups have six or less carbon atoms
20 present such as vinyl, allyl, ethynyl, isopropenyl, etc.

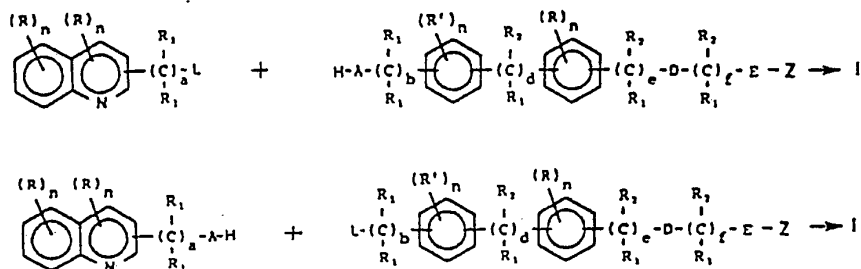
"Aralkyl" means an alkyl group substituted by an aryl radical. The preferred aralkyl groups are benzyl or phenethyl.

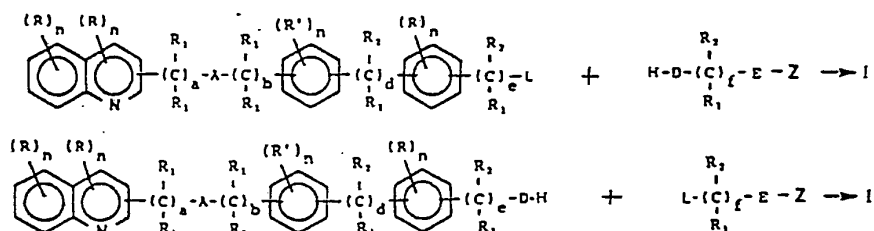
25 "Cycloalkyl" means a saturated monocyclic hydrocarbon ring having 3 to about 6 carbon atoms such as cyclopropyl, cyclohexyl, etc.

30 "Acyl" means an organic radical derived from an organic acid by removal of its hydroxyl group. Preferred acyl groups are acetyl, propionyl, benzoyl, etc.

"Halo" means a halogen. Preferred halogens include, chloride, bromide and fluoride. The preferred haloalkyl group is trifluoromethyl.

- 5 The compounds of this invention may be prepared in segments as is common to a long chain molecule. Thus it is convenient to synthesize these molecules by employing condensation reactions at the A and D cites of the molecule or at the bridge between the two phenyl rings. For this reason the
- 10 present compounds may be prepared by art recognized procedures from known compounds or readily preparable intermediates. Exemplary general procedures are as follows where Z is -CN, -COOR₁ or tetrazolyl. Thus in order to prepare compound of formula I, the following reactions or
- 15 combinations of reactions may be employed:



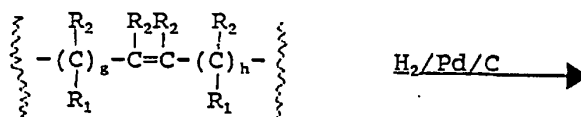
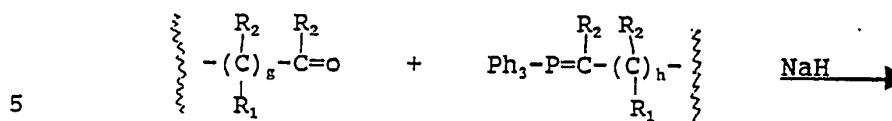


5 where:

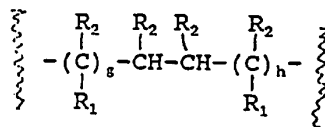
R, R', R₁, R₂, a, b, d, e, f, n, A, and D are as defined above; E is a chemical bond; Z is -CN, -COOR₁ or tetrazolyl, and L is a leaving group, such as halo, tosylate, or mesylate.

- 10 Reaction temperatures are in the range of room temperature to reflux and reaction times vary from 2 to 48 hours. The reaction is usually carried out in a solvent that will dissolve both reactants and is inert to both as well. Solvents include, but are not limited to, diethyl ether, tetrahydrofuran, N,N-dimethyl formamide, dimethyl sulfoxide, dioxane and the like.
- 15

Wittig condensation also may take place as follows:



10

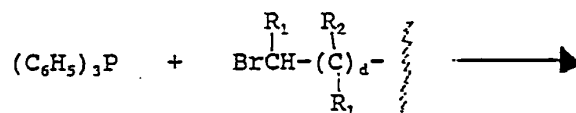


where $g + h$ is 0-3

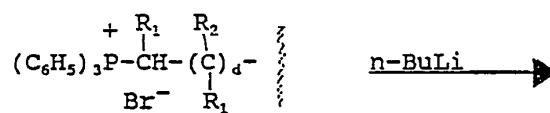
15 This may be carried out using normal Wittig reaction conditions. When the appropriate aldehyde or ketone is reacted with a Wittig reagent then condensation results in the formation of the double bond. This may then be reduced catalytically by known procedures such as Pd/C or any other
20 suitable hydrogenating condition.

The Wittig reagent is prepared by known art recognized procedures such as reaction of triphenyl phosphine or triethyl phosphite, with a substituted alkyl bromide followed
25 by treatment either with a strong organometallic or alkoxide base such as n-BuLi or NaOH, or heating to reflux for an appropriate period of time, respectively.

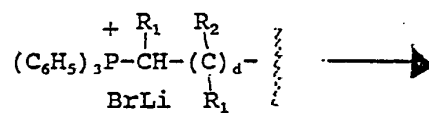
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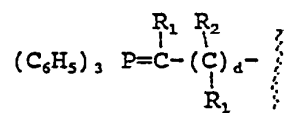
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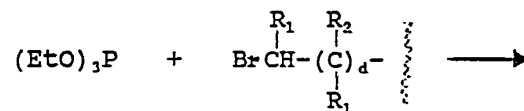
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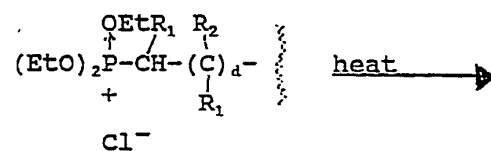
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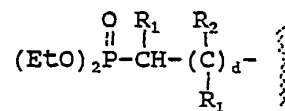
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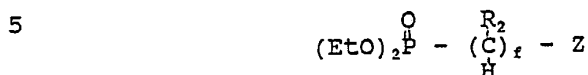
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Those compounds where D and/or E are $\begin{smallmatrix} R_1 \\ -C= \\ R_1 \end{smallmatrix}$ are also prepared by reacting the appropriate aldehyde or ketone with a substituted Wittig reagent of the formula



where Z is cyano or carbalkoxy.

10 The tetrazole may be formed from the nitrile at various stages of the synthesis by treatment with hydrazoic acid formed in situ from sodium azide and an acid.

The products of this invention may be obtained as racemic
15 mixtures of their dextro and levorotatory isomers since at least one asymmetric carbon atom may be present. When two asymmetric carbon atoms are present the product may exist as a mixture of two diastereomers based on syn and anti configurations. These diastereomers may be separated by
20 fractional crystallization. Each diastereomer may then be resolved into dextro and levorotatory optical isomers by conventional methods.

Resolution may best be carried out in the intermediate
25 stage where it is convenient to combine the racemic compound with an optically active compound by salt formation, ester formation, or amide formation to form two diasteromeric products. If an acid is added to an optically active base, then two diastereomeric salts are produced which possess
30 different properties and different solubilities and can be separated by fractional crystallization. When the salts have been completely separated by repeated crystallization, the base is split off by acid hydrolysis and the pure d and l acids are obtained.

35 The present compounds form salts with acids when a basic amino function is present and salts with bases when an acid

function, i.e., carboxyl, is present. All such salts are useful in the isolation and/or purification of the new products. Of particular value are the pharmaceutically acceptable salts with both acids and bases. Suitable acids include, for example, hydrochloric, sulfuric, nitric, benzenesulfonic, toluenesulfonic, acetic, malic, tartaric and the like which are pharmaceutically acceptable. Basic salts for pharmaceutical use are the Na, K, Ca and Mg salts.

- 10 Various substituents on the present new compounds, e.g., as defined in R, R₁ and R₂ can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by known methods of substitution or conversion reactions. If the substituents themselves are reactive, then the substituents can themselves be protected according to the techniques known in the art. A variety of protecting groups known in the art, may be employed. Examples of many of these possible groups may be found in "Protective Groups in Organic Synthesis" by T. W. Green, John Wiley and Sons, 1981. For example, nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Acyl groups can be substituted onto the aryl groups by Friedel-Crafts acylation. The acyl groups can then be transformed to the corresponding alkyl groups by various methods, including the Wolff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono and dialkylamino groups; and mercapto and hydroxy groups can be alkylated to form corresponding ethers. Primary alcohols can be oxidized by oxidizing agents known in the art to form carboxylic acids or aldehydes, and secondary alcohols can be oxidized to form ketones. Thus, substitution or alteration reactions can be employed to provide a variety of substituents throughout the molecule of the starting material, intermediates, or the final product.

The compounds of the present invention have potent activity as leukotriene antagonists and as such possess therapeutic value in the treatment of inflammatory conditions and allergic responses such as anaphylaxis and asthma.

5 Protocol for SRS-A (slow reacting substance of anaphylaxis) Antagonists

Leukotrienes, the products of the 5-lipoxygenase pathway of arachidonic acid metabolism, are potent contractile agents with a variety of smooth muscle preparations. Thus, it has been hypothesized that the leukotrienes contribute significantly to the pathophysiology of asthma. This protocol describes an in vitro assay used to test compounds which specifically antagonize the actions of leukotrienes.

15 Peripheral strips of guinea pig lungs are prepared and hung in tissue baths (Metro #ME-5505, 10 ml) according to the published procedure - (Proc. Nat'l. Acad. Sci., U.S.A. Volume 77, pp. 4354-4358, 1980). The strips are thoroughly rinsed in Assay Buffer and then connected with surgical silk thread support rods from the tissue baths. The rods are adjusted in the baths and the strips connected to the pressure transducers (Grass FT 103 or Gould US-3). The tissue baths are aerated with 95% oxygen - 5% carbon dioxide and maintained at 37°C. The assay buffer has been made as follows: for each liter of buffer the following are added to approximately 800 ml of water distilled in glass-6.87 g NaCl, 0.4 g $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, and 2.0 g D-glucose. Then a solution of 0.368 g $\text{CaCl}_2 \cdot \text{H}_2\text{O}$ in 100 ml glass-distilled water is slowly added to the buffer. Sufficient water is added to adjust the volume to 1 liter, and the solution is aerated with 95% oxygen - 5% carbon dioxide. Usually 10 liters of buffer are used for an experiment with 4 tissues. After the tissues have been repeatedly washed and allowed to equilibrate in the tissue bath, they are challenged with 1 μM histamine. After maximum contractions have been obtained, the tissues are

washed and allowed to relax back to baseline tension. This histamine challenge procedure is repeated at least 1 to 2 more times to obtain a repeatable control response. The average response to $1 \mu\text{M}$ histamine for each tissue is used to
5 normalize all other challenges.

Responses of each tissue to a predetermined concentration of leukotriene are then obtained. Usually test compounds are examined initially at $30 \mu\text{M}$ on resting tension
10 of the tissues without any added agonist or antagonist to determine if the compound has any possible intrinsic activity. The tissues are washed and the test compound is added again. Leukotriene is added after the desired pre-incubation time. The intrinsic activity of the compounds,
15 and their effect on leukotriene-induced contractions are then recorded.

The results of this test for of the compounds of the this invention indicates that these compounds are considered to be
20 useful leukotriene antagonists.

Inhibitions of (^3H)-LTD₄ Binding Membranes from Guinea Pig Lung.

25 A. Preparation of the Crude Receptor Fraction

This procedure was adapted from Mong *et al.* 1984. Male guinea pigs are sacrificed by decapitation and their lungs are quickly removed and placed in a beaker containing ice-cold homogenization buffer. The lungs are separated from
30 connective tissue, minced with scissors, blotted dry and weighed. The tissue is then homogenized in 40 volumes (w/v) of homogenization buffer with a Polytron at a setting of 6 for 30 seconds. The homogenate is centrifuged at $1000 \times g$ for 10 minutes (e.g. 3500 RPM, SS-34 Rotor). The supernatant
35 is filtered through two layers of cheese cloth and centrifuged at $30,000 \times g$ for 30 minutes (e.g. 18,500 RPM SS-34 Rotor), after which the resulting pellet is resuspended in

20 volumes of assay buffer by hand homogenization using a Dounce homogenizer. The final pellet is resuspended in 10 volumes of assay buffer and kept at 4°C until use.

5 B. Binding Assay:

Each assay tube (16 x 100 mm) contains the following:

490 μ l Assay Buffer

10 μ l Test compound or solvent

100 μ l ^3H -LTD, (ca. 17,500 DMP)

10 400 μ l Protein preparation

Incubations are done at 25°C for 20 minutes in a shaking water bath. Reactions are started by the addition of the protein preparation. At the end of the incubation time, 4.0 ml of cold wash buffer is added to the tube. After being
15 vortexed, the contents of the tube are immediately poured over a Whatman GF/C Filter (25 mm diameter) which is sitting in a vacuum manifold (e.g., Millipore Model No. 3025 manifold) to which a partial vacuum is applied. The filters are immediately washed with an additional 15 ml of cold
20 buffer. The filters are transferred to 7 ml plastic scintillation vials to which 6.0 ml of appropriate scintillation fluid (e.g., Scintiverse) is added. After being allowed to equilibrate for 4-6 hours, the radioactivity is counted with a liquid scintillation counter appropriately
25 set for tritium.

The required control assay tubes include the following:

(a) Total Binding: No test compound is added; buffer is substituted.

30 (b) Non-Specific Binding: Non-labeled ligand is added at a concentration of 1 μ M.

(c) Solvent Controls: If test compound is dissolved in a solvent, controls for both Total Binding and Non-Specific Binding containing solvent but no compounds are required.

35 The results of this test indicate that the compounds for this invention exhibit valuable properties which are useful

in the treatment of inflammatory conditions and allergic responses.

The compounds of the present invention can be administered
5 to a mammalian host in a variety of forms adapted to the
chosen route of administration, i.e., orally, or
parenterally. Parenteral administration in this respect
includes administration by the following routes:
intravenous, intramuscular, subcutaneous, intraocular,
10 intrasynovial, transeptheliaily including transdermal,
ophthalmic, sublingual and buccal; topically including
ophthalmic, dermal, ocular, rectal and nasal inhalation via
insufflation and aerosol.

15 The active compound may be orally administered, for
example, with an inert diluent or with an assimilable edible
carrier, or it may be enclosed in hard or soft shell gelatin
capsules, or it may be compressed into tablets, or it may be
incorporated directly with the food of the diet. For oral
20 therapeutic administration, the active compound may be
incorporated with excipient and used in the form of
ingestible tablets, buccal tablets, troches, capsules,
elixirs, suspensions, syrups, wafers, and the like. Such
compositions and preparations should contain at least 0.1% of
25 active compound. The percentage of the compositions and
preparations may, of course, be varied and may conveniently
be between about 2 to about 6% of the weight of the unit.
The amount of active compound in such therapeutically useful
compositions is such that a suitable dosage will be obtained.
30 Preferred compositions or preparations according to the
present invention are prepared so that an oral dosage unit
form contains between about 50 and 300 mg of active compound.

35 The tablets, troches, pills, capsules and the like may also
contain the following: A binder such as gum tragacanth,
acacia, corn starch or gelatin; excipients such as dicalcium

phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations.

The active compound may also be administered parenterally or intraperitoneally. Solutions of the active compound as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersion can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It may be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and

fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils.

5 The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, 10 phenol, sorbic acid, thimersal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions of agents delaying absorption, 15 for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated 20 above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case 25 of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

30 The therapeutic compounds of this invention may be administered to a mammal alone or in combination with pharmaceutically acceptable carriers, as noted above, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of 35 administration and standard pharmaceutical practice.

The physician will determine the dosage of the present therapeutic agents which will be most suitable for prophylaxis or treatment and it will vary with the form of administration and the particular compound chosen, and also, it will vary with the particular patient under treatment. He will generally wish to initiate treatment with small dosages by small increments until the optimum effect under the circumstances is reached. The therapeutic dosage will generally be from 0.1 to 100 μ M/day or from about 0.1 mg to about 50 mg/kg of body weight per day and higher although it may be administered in several different dosage units. Higher dosages are required for oral administration.

The compounds of the present invention may be prepared by the following representative examples.

EXAMPLE 1

METHYL 3-(4-HYDROXYBENZYL) BENZOATE

Methyl 3-(4-hydroxybenzoyl)benzoate (0.1 mol) in absolute ethanol (500 ml) is shaken under 50 psi of hydrogen in the presence of 10% palladium on carbon (2 g). After consumption of the starting material the suspension is filtered and evaporated to give methyl 3-(4-hydroxybenzyl)benzoate

EXAMPLE 2

When methyl 3-(4-hydroxybenzoyl)benzoate of Example 1 is replaced by the compounds of Table I below, then the corresponding product is prepared.

TABLE I

ethyl 3-(4-hydroxybenzoyl)benzoate
methyl 2-(4-hydroxybenzoyl)benzoate
methyl 3-(3-hydroxybenzoyl)benzoate
methyl 4-(3-hydroxybenzoyl)benzoate
methyl 4-(4-hydroxybenzoyl)benzoate

- methyl 3-(2-hydroxybenzoyl)benzoate
methyl 3-(4-methoxy-3-hydroxybenzoyl)benzoate
methyl 3-(3-methyl-4-hydroxybenzoyl)benzoate
methyl 3-(2-methyl-4-hydroxybenzoyl)benzoate
5 methyl 4-(3-methyl-4-hydroxybenzoyl)benzoate
methyl 3-(4-methyl-3-hydroxybenzoyl)benzoate
methyl 3-(5-methyl-3-hydroxybenzoyl)benzoate
methyl 3-(4-hydroxybenzoyl)-4-methylbenzoate
methyl 4-(4-hydroxybenzoyl)-2-methylbenzoate
10 methyl 4-(4-hydroxybenzoyl)-3-methylbenzoate
methyl 4-(4-hydroxybenzoyl)-2-methoxybenzoate
methyl 4-(4-hydroxybenzoyl)-3-methoxybenzoate
methyl 4-(4-hydroxybenzoyl)-5-methylbenzoate
methyl 3-(3-hydroxybenzoyl)-4-methoxybenzoate
15 methyl 3-(4-hydroxybenzoylmethyl)benzoate
methyl 3-(2-(4-hydroxybenzoyl)ethyl)benzoate
methyl 3-(1-(4-hydroxybenzoyl)ethyl)benzoate
methyl 3-(3-(4-hydroxybenzoyl)propyl)benzoate
methyl 3-(2-(4-hydroxybenzoyl)propyl)benzoate
20 methyl 3-(1-(4-hydroxybenzoyl)propyl)benzoate
methyl 3-(4-(4-hydroxybenzoyl)butyl)benzoate
methyl 3-(3-(4-hydroxybenzoyl)butyl)benzoate
methyl 3-(2-(4-hydroxybenzoyl)butyl)benzoate
methyl 3-(1-(4-hydroxybenzoyl)butyl)benzoate
25 methyl 3-(4-(4-hydroxybenzoyl)-3,3-dimethylbutyl)-
benzoate
methyl 3-(3-cyclopropyl-2-(4-hydroxybenzoyl)butyl)-
benzoate
methyl 3-(2-phenyl-4-(4-hydroxybenzoyl)butyl)benzoate
30 methyl 4-(3-methoxy-2-(4-hydroxybenzoyl)propyl)-
benzoate
methyl 4-(3-dimethylamino-2-(3-hydroxybenzoyl)propyl)-
benzoate
methyl 4-(3-acetylamino-2-(3-hydroxybenzoyl)propyl)-
35 benzoate
methyl 4-(3-spiro-1'-cyclopentane-2-(4-hydroxy-
benzoyl)propyl)benzoate

- methyl 2-(3-carbomethoxy-2-(3-hydroxybenzoyl)propyl)-benzoate
- methyl 4-(3-benzylamino-2-(2-hydroxybenzoyl)butyl)-benzoate
- 5 methyl 3-(4-hydroxybenzoyl)phenoxyacetate
methyl 3-(4-hydroxybenzoyl)phenoxypropionate
methyl 4-(3-hydroxybenzoyl)phenoxyacetate
methyl 4-(3-hydroxybenzoyl)phenoxypropionate
methyl 3-(3-hydroxybenzoyl)phenoxyacetate
10 methyl 3-(3-hydroxybenzoyl)phenoxypropionate
methyl 4-(4-hydroxybenzoyl)phenoxyacetate
methyl 4-(4-hydroxybenzoyl)phenoxypropionate
methyl 3-(4-hydroxybenzoyl)phenylacetate
methyl 3-(4-hydroxybenzoyl)phenylpropionate
15 methyl 3-(4-hydroxybenzoyl)phenylbutyrate
methyl 3-(4-hydroxybenzoyl)benzonitrile
methyl 5-(3-(4-hydroxybenzoyl)phenyl)tetrazole
ethyl 4-(4-methoxy-3-hydroxybenzoyl)benzoate
methyl 4-(3-methoxy-4-hydroxybenzoyl)benzoate
20 methyl 3-(3-methyl-4-hydroxybenzoyl)-4-methylbenzoate
methyl 3-(4-hydroxybenzoyl)-4-methoxybenzoate
methyl 3-(4-hydroxybenzoyl)-5-methoxybenzoate
methyl 4-(4-hydroxybenzoyl)-2-methoxybenzoate
methyl 4-(4-hydroxybenzoyl)-3-carbomethoxybenzoate
25 methyl 3-(4-hydroxybenzoyl)-4-ethoxybenzoate
methyl 3-(4-mercaptobenzoyl)benzoate
methyl 4-(3-mercaptobenzoyl)benzoate
methyl 3-(3-mercaptobenzoyl)benzoate
methyl 4-(4-mercaptobenzoyl)benzoate
30 methyl 2-(4-mercaptobenzoyl)benzoate
methyl 3-(4-mercaptobenzoyl)benzoate

EXAMPLE 335 METHYL 3-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZOATE

A mixture of methyl 3-(4-hydroxybenzyl)benzoate (0.08 mol), 2-chloromethylquinoline (0.10 mol) and potassium carbonate

(anhydrous, 0.10 mol) are heated at reflux in a 7:1 mixture of acetone:dimethylformamide (600 ml) until all the benzoate starting material is consumed. The reaction is then filtered, evaporated and the residue diluted with water and
5 extracted with ethyl acetate. The ethyl acetate extracts are dried (magnesium sulfate), evaporated and then applied to a silica gel column. Elution with ethyl acetate:petroleum ether gives methyl 3-(4-(2-quinolinylmethoxy)benzyl)-benzoate.

10

EXAMPLE 4

When 2-quinolinylmethyl chloride of Example 3 above is replaced by the quinoline compounds of Table II below then the corresponding product is obtained.

15

TABLE 2

	2-chloromethylquinoline
	2-bromomethylquinoline
	2-(1-chloroethyl)quinoline
20	2-(2-chloroethyl)quinoline
	2-bromoethylquinoline
	3-chloromethylquinoline
	4-chloromethylquinoline
	2-(β -chloroethyl)quinoline
25	2-(β -chloropropyl)quinoline
	2-(β -chloro- β -phenethyl)quinoline
	2-chloromethyl-4-methylquinoline
	2-chloromethyl-6-methylquinoline
	2-chloromethyl-8-methylquinoline
30	2-chloromethyl-6-methoxyquinoline
	2-chloromethyl-6-nitroquinoline
	2-chloromethyl-6,8-dimethylquinoline

EXAMPLE 53-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZOIC ACID

5 Methyl 3-(4-(2-quinolinylmethyloxy)benzyl)benzoate (0.05 mol) is heated at reflux in a 9:1 mixture of ethanol and 0.5 N aqueous NaOH (450 ml). After several hours the clear reaction is evaporated. The solid residue is taken up in water and acidified. The resulting crystalline product is
10 isolated by filtration and dried by suction with a rubber dam to obtain 3-(4-(2-quinolinylmethyloxy)benzyl)benzoic acid.

In a similar manner the acids of this invention may be prepared.

15

EXAMPLE 63-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZOYL CHLORIDE .

To (0.05 mol) of 3-(4-(2-quinolinylmethyloxy)benzyl)-benzoic acid in dichloromethane solution (500 ml) and chilled
20 in an ice bath is added thionyl chloride (0.06 mol) and a few drops of dimethylformamide. Upon completion of the reaction, the clear solution is evaporated to give 3-(4-(2-quinolinylmethyloxy)benzyl)benzoyl chloride.

25 In a similar manner the acid halides of this invention may be prepared.

EXAMPLE 73-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZAMIDE

3-(4-(2-Quinolinylmethyloxy)benzyl)benzoyl chloride (0.05 mol) in tetrahydrofuran (300 ml) is treated with concentrated ammonium hydroxide (25 ml). The reaction
mixture is stirred overnight at room temperature and then
35 evaporated and partitioned between ethyl acetate and water. The ethyl acetate fraction is dried and evaporated to give 3-(4-(2-quinolinylmethyloxy)benzyl)benzamide.

In a similar manner the amides of this invention may be prepared.

5

EXAMPLE 83-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZONITRILE

3-(4-(2-Quinolinylmethyloxy)benzyl)benzamide (0.03 mol) in pyridine (150 ml) with methane sulfonyl chloride (0.06 mol) is heated at 70°C for several hours. The reaction mixture is poured into ice water and extracted with ethyl acetate. The ethyl acetate extract is dried (magnesium sulfate) then applied to a silica gel column. The product is isolated by elution with the appropriate mixture of ethyl acetate and petroleum ether to obtain 3-(4-(2-quinolinylmethyloxy)benzyl)benzonitrile.

In a similar manner the nitriles of this invention may be prepared.

20

EXAMPLE 95-(3-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) PHENYL) TETRAZOLE

A mixture of sodium azide (0.03 mol), ammonium chloride (0.03 mol) and 3-(4-(2-quinolinylmethyloxy)benzyl)benzonitrile (0.01 mol) in dimethylformamide (20 ml) are heated at 100°C for 18 hours. The reaction is poured into aqueous 10% sodium hydroxide solution and washed with ethyl acetate. The crystalline product is isolated by acidification and filtration to obtain 5-(3-(4-(2-quinolinylmethyloxy)benzyl)phenyl)tetrazole.

EXAMPLE 10

When the procedures of 1-9 are followed and the starting materials are selected from Table I of Example 2 and Table II of Example 4, then the corresponding products are obtained.

A representative list of compounds so prepared are shown below in Table III.

TABLE III

5	5-(3-(3-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
	5-[3-(4-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
	5-[2-(4-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
	5-[4-(4-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
10	5-[2-(3-(2-quinolinylmethyloxy)benzyl)phenyl]tetrazole
	5-[3-(3-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
	5-[3-(4-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
	5-[2-(3-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
15	5-[4-(4-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
	5-[2-(4-(2-quinolinylmethyloxy)benzyl)benzyl]tetrazole
	5-[2-(3-(4-(2-quinolinylmethyloxy)benzyl)phenyl)propyl]-tetrazole
	5-[2-(3-(4-(2-quinolinylmethyloxy)benzyl)phenyl)butyl]-tetrazole
20	5-[3-(3-(4-(2-quinolinylmethyloxy)benzyl)phenyl)butyl]-tetrazole
	5-[3-(3-(2-quinolinylmethylthio)benzyl)phenyl]tetrazole
	5-[3-(3-(2-quinolinylmethylthio)phenethyl)phenyl]tetrazole
25	5-[3-(3-(2-quinolinylmethyloxy)phenylpropyl)phenyl]-tetrazole
	5-[4-(3-(2-quinolinylmethyloxy)phenylbutyl)-3-methoxyphenyl]tetrazole
	5-[3-(3-(2-quinolinylmethyloxy)benzyl)-4-methoxyphenyl]-tetrazole
30	5-[4-(4-(2-quinolinylmethyloxy)benzyl)-3-methoxyphenyl]-tetrazole
	5-[3-(4-(2-quinolinylmethyloxy)benzyl)-4-methoxyphenyl]-tetrazole
35	5-[4-(3-(2-quinolinylmethyloxy)benzyl)-3-methoxyphenyl]-tetrazole

- 5-[4-(3-(2-quinolinylmethoxy)benzyl)-3-carbomethoxy-phenyl]tetrazole
- 5-[4-(3-(2-quinolinylmethoxy)benzyl)-3-methoxybenzyl]-tetrazole
- 5 5-[3-(3-(2-quinolinylmethoxy)benzyl)-4-methoxybenzyl]-tetrazole
- 5-[3-(4-(2-quinolinylmethoxy)benzyl)-4-methoxybenzyl]-tetrazole
- 10 5-[4-(4-(2-quinolinylmethoxy)benzyl)-3-methoxybenzyl]-tetrazole
- 5-[4-(4-(2-quinolinylmethoxy)benzyl)-3-carbomethoxybenzyl]tetrazole
- 5-[4-(3-(2-quinolinylmethoxy)benzyl)-3-carbomethoxybenzyl]tetrazole
- 15 5-[4-(3-(2-quinolinylmethoxy)-4-methylbenzyl)phenyl]-tetrazole
- 5-[3-(4-(2-quinolinylmethoxy)-3-methylbenzyl)phenyl]-tetrazole
- 5-(3-methyl-4-(3-(3-(2-quinolinylmethoxy)phenethyl)-phenyl)butyl)tetrazole
- 20 5-(2-(4-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 5-(4-(3-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 5-(3-(4-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 5-(4-(4-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 25 5-(3-(3-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 5-(2-(3-(2-quinolinylmethoxy)phenethyl)phenyl)tetrazole
- 5-(2-(4-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole
- 5-(3-(4-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole
- 5-(4-(4-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole
- 30 5-(2-(3-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole
- 5-(3-(3-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole
- 5-(4-(3-(2-quinolinylmethoxy)phenethyl)benzyl)tetrazole

EXAMPLE 113-(2-QUINOLINYLMETHLOXY) BENZALDEHYDE

- 5 A solution of 0.65 g (5.4 mmol) 3-hydroxybenzaldehyde, 0.94 g (5.3 mmol) of 2-quinolinylmethylchloride, and 0.75 g (5.4 mmol) of potassium carbonate in 15 ml of DMF is heated at 60°C overnight. The reaction mixture is poured into water. The precipitated product is collected on a filter and
- 10 purified by dry column chromatography to give 3-(2-quinolinylmethoxy)benzaldehyde.

EXAMPLE 12

- 15 When 3-hydroxybenzaldehyde of Example 11 is replaced by the compounds of Table IV below, then the corresponding product is obtained.

TABLE IV

- | | |
|----|--------------------------------------|
| 20 | 2-hydroxybenzaldehyde |
| | 3-hydroxybenzaldehyde |
| | 4-hydroxybenzaldehyde |
| | 2-methyl-3-hydroxybenzaldehyde |
| | 5-methyl-3-hydroxybenzaldehyde |
| 25 | 2-methyl-4-hydroxybenzaldehyde |
| | 3-methyl-4-hydroxybenzaldehyde |
| | 5-methoxy-3-hydroxybenzaldehyde |
| | 4-methoxy-3-hydroxybenzaldehyde |
| | 2-methoxy-3-hydroxybenzaldehyde |
| 30 | 5-carbomethoxy-3-hydroxybenzaldehyde |
| | 3-hydroxyphenylacetaldehyde |
| | 4-hydroxyphenylacetaldehyde |
| | 3-hydroxyphenylpropionaldehyde |
| | 4-hydroxyphenylpropionaldehyde |
| 35 | 3-hydroxyphenylisopropionaldehyde |
| | 4-hydroxyphenylisopropionaldehyde |

28

3-hydroxyphenylbutyraldehyde
4-hydroxyphenylbutyraldehyde
3-mercaptopbenzaldehyde
4-mercaptopbenzaldehyde
5 3-hydroxyphenyl- α -methylbutyraldehyde
3-hydroxyphenyl- β -methylbutyraldehyde
4-hydroxyphenyl- α -methylbutyraldehyde
4-hydroxyphenyl- β -methylbutyraldehyde

10

EXAMPLE 13

When 2-quinolinylmethyl chloride of Examples 11 and 12 are replaced by the compounds of Example 4, Table II, then the corresponding products are obtained.

15

EXAMPLE 144-(3-(3-(2-QUINOLINYLMETHYLOXY)PHENYL)-1-OXO-2-PROPEN-1-YL)-BENZONITRILE

20 4-Cyanoacetophenone (0.01 mol) in ethanol (100 ml) is added dropwise to a 0°C mixture of 3-(2-quinolinylmethyl-oxy)-benzaldehyde (0.01 mol) and sodium ethoxide (0.001 mol) in ethanol (200 ml). The reaction mixture is allowed to thaw to ambient temperature and after several hours it is evaporated and partitioned between ethyl acetate and water. The ethyl
25 acetate fraction is dried and evaporated to give 4-(3-(3-(2-quinolinylmethyloxy)phenyl)-1-oxo-2-propen-1-yl)-benzonitrile.

EXAMPLE 15

30

When 3-(2-quinolinylmethyloxy)benzaldehyde of Example 14 is replaced by the compounds formed in Examples 12 and 13, then the corresponding product is obtained.

EXAMPLE 164-(3-(3-(2-QUINOLINYLMETHYLOXY) PHENYL) PROPYL) BENZONITRILE

5 A solution of 4-(3-(3-(2-quinolinylmethyloxy)phenyl)-1-oxo-2-propen-1-yl)benzonitrile (0.008 mol) in ethyl acetate (150 ml) is shaken under 50 psi of hydrogen gas in the presence of 10% palladium on carbon catalyst (1.0 g). The reaction is filtered through a celite pad and evaporated to give 4-(3-(3-

10 (2-quinolinylmethyloxy)phenyl)propyl)benzonitrile.

EXAMPLE 17

15 5-(4-(3-(3-(2-QUINOLINYLMETHYLOXY) PHENYL) PROPYL) PHENYL) - TETRAZOLE

4-(3-(3-(2-Quinolinylmethyloxy)phenyl)propyl)benzonitrile (0.006 mol) with sodium azide (0.018 mol) and ammonium chloride (0.018 mol) in dimethylformamide (15 ml) is heated at 100°C for 18 hours. The reaction mixture is poured into

20 10% aqueous sodium hydroxide solution and washed with ethyl acetate. The aqueous layer is acidified to pH 6 with 1 N aqueous HCl and the solid which precipitates is collected to obtain 5-(4-(3-(3-(2-quinolinylmethyloxy)-

phenyl)propyl)phenyl)tetrazole.

25

EXAMPLE 18

When the compounds obtained in Example 13 are used as the starting materials in Example 14, then the corresponding products are obtained. Representative compounds so obtained

30 are shown in Table V, below.

TABLE V

35 5-(4-(3-(4-(2-quinolinylmethyloxy)phenyl)propyl)-phenyl)tetrazole

5-(3-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)-

- phenyl) tetrazole
- 5-(2-(3-(4-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) tetrazole
- 5 5-(2-(3-(3-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) tetrazole
- 5-(4-(4-(3-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 10 5-(4-(3-(3-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 5-(4-(2-(3-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 5-(3-(3-(4-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 15 5-(4-(4-(4-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 5-(3-(3-(3-(2-quinolinylmethyloxy) phenyl) butyl) -
phenyl) tetrazole
- 20 5-(2-(4-(3-(4-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) ethyl) tetrazole
- 5-(3-(4-(3-(4-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) propyl) tetrazole
- 5-(2-(4-(3-(4-(2-quinolinylmethyloxy) phenyl) propyl) -
phenyl) propyl) tetrazole
- 25 5-(3-(3-(2-quinolinylmethyloxy) α -methylphenethyl) -
phenyl) tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy) β -methylphenethyl) -
phenyl) tetrazole
- 30 5-(4-(3-(2-quinolinylmethyloxy) α -methylphenethyl) -
phenyl) tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy) β -methylphenethyl) -
phenyl) tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy) α -methylphenethyl) -
phenyl) tetrazole
- 35

- 5-(4-(4-(2-quinolinylmethyloxy) β -methylphenethyl)-phenyl)tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy) α -methylphenethyl)-phenyl)tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy) β -methylphenethyl)-phenyl)tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy) α -methylphenethyl)-benzyl)tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy) β -methylphenethyl)-benzyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy) α -methylphenethyl)-benzyl)tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy) β -methylphenethyl)-benzyl)tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy) α -methylphenethyl)-benzyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)benzyl)phenyl)-tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)benzyl)-tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenethyl)-tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)benzyl)benzyl)-tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenethyl)-tetrazole
- 5-(4-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)-benzyl)tetrazole
- 5-(4-(3-(4-(2-quinolinylmethyloxy)phenyl)propyl)-benzyl)tetrazole
- 5-(4-(4-(3-(4-(2-quinolinylmethyloxy)phenyl)propyl)-phenyl)butyl)tetrazole
- 5-(3-(4-(3-(4-(2-quinolinylmethyloxy)phenyl)propyl)-phenyl)butyl)tetrazole

5-(2-(4-(3-(4-(2-quinolinylmethyloxy)phenyl)propyl)-phenyl)butyl)tetrazole

EXAMPLE 19

5 4-(4-(2-QUINOLINYL METHYLOXY) STYRYL) BENZONITRILE

A suspension of 5.51 g (13.29 mmol) of (4-cyanobenzyl)-triphenylphosphonium chloride in 100 ml of dry DMF under positive nitrogen atmosphere is cooled to 0°C and 0.50 g (20.77 mmol), of an 80% NaH in oil dispersion is added in
 10 small portions. The suspension is aged for 15 minutes at 0°C followed by 45 minutes at room temperature to assure complete anion formation. The flask is cooled back to 0°C and 3.5 g (13.29 mmol) of 4-(2-quinolinylmethyloxy)benzaldehyde in 20 ml of DMF is dropped in over a period of 15 minutes. The
 15 reaction is allowed to equilibrate to room temperature and stirred for 2 hours. The resultant mixture is poured into ice water and filtered. The precipitate is dissolved in CH₂Cl₂, dried, and concentrated in vacuo. The crude product is recrystallized from ether to give 4-(4-(2-
 20 quinolinylmethyloxy)styryl)benzonitrile. (M.P. 116°C-118°C.)

EXAMPLE 20

When (4-cyanobenzyl)triphenylphosphonium chloride of
 25 Example 19 is replaced by the compounds of Table VI below then the corresponding products are prepared.

TABLE VI

30	2-cyanobenzyl triphenylphosphonium chloride
	3-cyanobenzyl triphenylphosphonium chloride
	4-cyanobenzyl triphenylphosphonium chloride
	3-cyano-4-methylbenzyl triphenylphosphonium chloride
	4-cyano-3-methylbenzyl triphenylphosphonium chloride
35	3-cyanomethylbenzyl triphenylphosphonium chloride
	4-cyanomethylbenzyl triphenylphosphonium chloride

- 3-cyanoethylbenzyl triphenylphosphonium chloride
4-cyanoethylbenzyl triphenylphosphonium chloride
3-cyanopropylbenzyl triphenylphosphonium chloride
4-cyanopropylbenzyl triphenylphosphonium chloride
5 3-(2-cyanopropyl)benzyl triphenylphosphonium chloride
4-(2-cyanopropyl)benzyl triphenylphosphonium chloride
3-(2-cyanobutyl)benzyl triphenylphosphonium chloride
4-(2-cyanobutyl)benzyl triphenylphosphonium chloride
3-(3-cyanobutyl)benzyl triphenylphosphonium chloride
10 4-(3-cyanobutyl)benzyl triphenylphosphonium chloride
3-cyanophenylethyl triphenylphosphonium chloride
4-cyanophenylethyl triphenylphosphonium chloride
3-(2-cyanopropylthio)benzyl triphenylphosphonium
chloride
15 3-(2-cyanopropoxy)benzyl triphenylphosphonium
chloride
3-(2-cyanopropyl-N-methylamino)benzyl triphenyl-
phosphonium chloride
3-(3-cyanopropoxy)benzyl triphenylphosphonium
20 chloride

EXAMPLE 21

- When the Wittig reagents of Table VI, Example 20 are
25 reacted with the compounds prepared by Example 13 following
the procedure of Example 19 then the corresponding products
are obtained.

EXAMPLE 22

- 30 4-(4-(2-QUINOLINYLMETHYLOXY) PHENETHYL) BENZONITRILE

- A mixture of 0.75 g (2.07 mmol) of (4-(4-(2-quinolinyl-
methyloxy)styryl)benzonitrile and 0.08 g of 10% Pd on carbon
in 75 ml of ethanol is shaken for 1.5 hours under 30 PSI of
hydrogen. The mixture is filtered through a bed of celite
35 and the filtrate concentrated in vacuo. Trituration with
ether gives a precipitate which is filtered off and

34

recrystallized from methylene chloride-ether to give 4-(4-(2-quinolinylmethyloxy)phenethyl)benzonitrile. (M.P. 156°C - 158°C.)

5

EXAMPLE 235-(4-(4-(2-QUINOLINYL METHYLOXY) PHENETHYL) PHENYL) TETRAZOLE

A mixture of 0.35 g (0.96 mmol) of 4-(4-(2-quinolinylmethyloxy)phenethyl)benzonitrile, 0.31 g (4.8 mmol, 5 equiv.)
10 of sodium azide, and 0.55 g (4.8 mmol, 5 equiv.) of pyridine hydrochloride in 15 ml of DMF are heated at 110°C for 48 hours. The mixture is poured into ice water and the precipitate that forms filtered off and recrystallized from methanol-water to obtain 5-(4-(4-(2-quinolinylmethyloxy)
15 phenethyl)phenyl)tetrazole. (M.P. 203°C - 206°C.)

EXAMPLE 24

When the procedures of Examples 22 and 23 are followed
20 using the compounds prepared by Examples 20 and 21 as the starting materials, then the corresponding products are obtained. A representative list of the compounds thus prepared is shown in Table VII below.

25

TABLE VII

5-(4-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-
butyl)tetrazole
5-(3-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-
30 butyl)tetrazole
5-(3-(4-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy)-
butyl)tetrazole
5-(2-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy)-
propyl)tetrazole
35 5-(3-(3-(3-(2-quinolinylmethylthio)phenethyl)phenyl)-
thio)butyl)tetrazole

- 5-(3-(3-(3-(2-quinolinylmethylthio)phenethyl)phenoxy)-
butyl)tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenethyl)-
5 tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)benzyloxy)phenethyl)-
tetrazole
- 5-(3-(3-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)-
phenyl)butyl)tetrazole
- 10 5-(2-(3-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
15 tetrazole
- 5-(2-(4-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
tetrazole
- 20 5-(4-(4-(2-quinolinylmethyloxy)benzyl)phenoxymethyl)-
tetrazole
- 5-(3-(3-(2-quinolinylmethyloxy)benzyl)phenoxyethyl)-
tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy)benzyl)phenoxyethyl)-
25 tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)benzyl)phenoxyethyl)-
tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)benzyl)phenoxyethyl)-
tetrazole
- 30 5-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-
methyl)tetrazole
- 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-
methyl)tetrazole
- 5-(3-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy-
35 methyl)tetrazole
- 5-(4-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy-
methyl)tetrazole

5-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-ethyl)tetrazole

5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-ethyl)tetrazole

5 5-(3-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy-ethyl)tetrazole

5-(4-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy-ethyl)tetrazole

10

EXAMPLE 253-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZOYL-N-BENZENE-SULFONAMIDE

15 A reaction mixture of 0.65 g of 3-(4-(2-quinolinylmethyloxy)benzyl)benzoic acid, 0.28 g of benzene-sulfonamide, 0.28 g of 4-dimethylpyridine, and 0.44 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimidehydrochloride in 50 ml of CH_2Cl_2 is stirred at room temperature overnight. The solvent is removed and the residue is extracted into ethyl acetate. The organic solution is washed with water, and
20 evaporated. The product is purified by dry column chromatography to give 3-(4-(2-quinolinylmethyloxy)benzyl)-benzoyl-N-benzenesulfonamide.

25

EXAMPLE 26

When 3-(4-(2-quinolinylmethyloxy)benzyl)benzoic acid of Example 25 is replaced by the acids of this invention such as those of Example 5 then the corresponding benzenesulfonamide
30 compound is prepared.

When benzenesulfonamide is replaced in the above Examples by a sulfonamide of the formula $\text{NH}_2\text{SO}_2\text{R}$, or an amine of the formula $\text{HN}(\text{R}_1)_2$, then the corresponding product is obtained.

EXAMPLE 273-(3-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZALDEHYDE

- 5 A solution of diisobutyl aluminum hydride (0.01 mol) in hexane is added dropwise to a solution of methyl 3-(3-(2-quinolinylmethyloxy)benzyl)benzoate (0.01 mol) in 100 ml of THF at 0°C. The reaction mixture is stirred at 0°C for 30 minutes and then quenched with methanol and Rochelle salt.
- 10 Extraction with ethyl acetate and purified by column chromatography gives 3-(3-(2-quinolinylmethyloxy)benzyl)-benzaldehyde.

EXAMPLE 28

- 15 When the esters of Examples 3 and 4 are used in place of methyl 3-(3-(2-quinolinylmethyloxy)benzyl)benzoate in Example 27 then the corresponding aldehyde is obtained.

EXAMPLE 293-(3-(2-QUINOLINYLMETHYLOXY) BENZYL) CINNAMYLNITRILE

- 20 Sodium hydride (60% oil dispersion, 1.2 g) and diethyl cyanomethylphosphonate (5 ml) are combined and stirred in THF (50 ml) for 5 minutes. This is then added to a THF solution of 3-(3-(2-quinolinylmethyloxy)benzyl)benzaldehyde (9.5 g).
- 25 The reaction mixture is stirred for an additional 30 minutes and poured into ice water. The crude product is filtered and chromatographed through a silica gel dry column using chloroform as the eluant to give 3-(3-(2-quinolinylmethyloxy)benzyl)cinnamyl nitrile.

30

EXAMPLE 30

When 3-(3-(2-quinolinylmethyloxy)benzyl)benzaldehyde of Example 29 is replaced by the compounds of Example 28, the corresponding product is prepared.

When diethylcyanomethylphosphonate in the above Example is replaced by diethylcyanoethylphosphate, diethylcyano-propylphosphate or diethylcyanoisopropylphosphate then the corresponding products are obtained.

EXAMPLE 31

10 5-(3-(3-(2-QUINOLINYL METHYLOXY) BENZYL) STYRYL) TETRAZOLE
HYDROCHLORIDE

A mixture of 3-(3-(2-quinolinylmethyl)benzyl)-cinnamyl nitrile (0.03 mol), anhydrous aluminum chloride (0.03 mol) and sodium azide (0.09 mol) in THF (30 ml) is stirred and refluxed for 18 hours. Hydrochloric acid (18% HCl 15 ml) is added and thereafter the reaction mixture is poured into ice water. The precipitate is collected and then recrystallized from methanol-ethyl acetate to obtain pure 5-(3-(3-(2-quinolinylmethyloxy)benzyl)styryl)tetrazole hydrochloride.

20 The free base is obtained by treatment of the salt with one equivalent of sodium hydroxide solution followed by removal of sodium chloride and water.

EXAMPLE 32

25 When 3-(3-(2-quinolinylmethyloxy)benzyl)cinnamyl nitrile of Example 31 is replaced by the compounds formed in Example 30, then the corresponding product is prepared. Representative compounds prepared by this invention are described in Table VIII.

30

TABLE VIII

5-(4-(3-(2-quinolinylmethyloxy)benzyl)styryl)tetrazole
5-(4-(3-(2-quinolinylmethyloxy)phenethyl)styryl)tetrazole
5-(3-(4-(2-quinolinylmethyloxy)benzyl)styryl)tetrazole

- 5-(4-(4-(2-quinolinylmethoxy)benzyl)styryl)tetrazole
5-(4-(3-(2-quinolinylmethoxy)-4-methylbenzyl)styryl)-
tetrazole
5-(4-(3-(2-quinolinylmethoxy)benzyl)3-methyl)styryl)-
5 tetrazole
5-(3-(3-(2-quinolinylmethylthio)benzyl)styryl)tetrazole
5-(3-(4-(2-quinolinylmethylthio)phenethyl)styryl)tetrazole
5-(3-(3-(4-(2-quinolinylmethoxy)phenyl)propyl)styryl)-
tetrazole
10 5-(3-(4-(3-(2-quinolinylmethoxy)benzyl)phenoxy)2-propen-
1-yl)tetrazole

EXAMPLE 33

- 15 ETHYL 5-(4-(3-(2-QUINOLINYL METHYLOXY) PHENETHYL) PHENYL)-
TETRAZOL-3-YL ACETATE

To a solution of 0.2 g sodium in 30 ml ethanol is first
added 1 g of 5-(4-(3-(2-quinolinylmethoxy)phenethyl)-
phenyl)tetrazole and then after 30 minutes 0.6 g of
20 ethylbromacetate and stirring is continued at 80°C for 16
hours. The solvent is then removed, diluted with water,
filtered, washed with ether and dried to give ethyl 5-(4-(3-
(2-quinolinylmethoxy)phenethyl)phenyl)tetrazol-3-yl
acetate.

- 25 When ethylbromoacetate in the above procedure is replaced
with N,N-diethyl- α -bromoacetamide, N,N-diethyl- aminoethyl
bromide or N-acetylaminoethyl bromide or N- acetyl- α -
bromoacetamide, then the corresponding products are obtained.

- 30 EXAMPLE 34

5-(4-(3-(2-QUINOLINYL METHYLOXY) PHENETHYL) PHENYL) TETRAZOL-3-
YL ACETIC ACID

- A mixture of 1 g of ethyl [5-(4-(3-(2-quinolinylmethyl-
35 oxy)phenethyl)phenyl)tetrazol-3-yl]acetate in 5 ml ethanol
and 40 ml of 1N NaOH is stirred at 70°C for 4 hours. This is

cooled, diluted with water, acidified with acetic acid, filtered, washed with water, and then ethyl acetate to give 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)tetrazol-3-yl acetic acid.

- 5 In a similar manner the substituted tetrazoles of this invention may be prepared.

EXAMPLE 35

10 4-(4-(2-QUINOLINYLMETHYLSULFINYL)PHENETHYL)BENZOIC ACID

- A. 4-(4-(2-quinolinylmethylthio)phenethyl)benzoic acid (4 mmol) in dichloroethene (50 ml) is stirred with m-chloroperbenzoic acid (4 mmol) and solid potassium hydrogen carbonate (1.0 g). The reaction is assayed by TLC and upon
15 consumption of the starting thio compound, the mixture is filtered, washed with dilute aqueous sodium bisulfite, dried and evaporated to give 4-(4-(2-quinolinylmethyl-sulfinyl)phenethyl)benzoic acid.

- 20 B. To 3 mmol of the sulfinyl compound from Step A in acetic acid (40 mmol) is added 30% hydrogen peroxide (2 ml). The mixture is stirred at ambient temperature and assayed by TLC. Upon disappearance of the sulfinyl starting compound, the reaction mixture is diluted with dichloromethane, washed
25 with dilute aqueous sodium bisulfite and water, dried and evaporated to give 4-(4-(2-quinolinylmethylsulfonyl)-phenethyl)benzoic acid.

- In a similar manner the sulfinyl and sulfonyl compounds of
30 this invention may be prepared.

EXAMPLE 365 4-(3-(3-(2-QUINOLINYL METHYLOXY) PHENYL)-1-OXO-2-PROPEN-1-YL)-
PHENOL

4-Hydroxyacetophenone (0.01 mol) in ethanol (100 ml) is added dropwise to a 0°C mixture of 3-(2-quinolinylmethyl-oxy)benzaldehyde (0.01 mol) and sodium ethoxide (0.00 mol) in ethanol (200 ml). The reaction mixture is allowed to thaw to
10 ambient temperature and after several hours it is evaporated and partitioned between ethyl acetate and water. The ethyl acetate fraction is dried and evaporated to give 4-(3-(3-(2-quinolinylmethyloxy)phenyl)-1-oxo-2-propen-1-yl)phenol.

15

EXAMPLE 37

When 4-hydroxy acetophenone of Example 36 is replaced with the compounds of Table IX below, then the corresponding phenol is prepared.

20

TABLE IX

	2-hydroxyacetophenone
	3-hydroxyacetophenone
	4-hydroxyacetophenone
25	3-methyl-4-hydroxyacetophenone
	4-methyl-3-hydroxyacetophenone
	2-methyl-4-hydroxyacetophenone
	4-methoxy-3-hydroxyacetophenone
	4-methoxy-2-hydroxyacetophenone
30	3-methoxy-4-hydroxyacetophenone
	2-methoxy-4-hydroxyacetophenone
	2-hydroxymethylacetophenone
	3-hydroxymethylacetophenone
	4-hydroxymethylacetophenone
35	3-hydroxypropylacetophenone
	4-hydroxypropylacetophenone

42

3-hydroxyisopropylacetophenone
4-hydroxyisopropylacetophenone
3-hydroxybutylacetophenone
4-hydroxybutylacetophenone
5 2-hydroxybutylacetophenone
3-(2-methyl)hydroxybutylacetophenone
3-(3-methyl)hydroxybutylacetophenone
4-(2-methyl)hydroxybutylacetophenone
4-(3-methyl)hydroxybutylacetophenone

10 EXAMPLE 38

When 3-(2-quinolinylmethyloxy)benzaldehyde of Example 36 is replaced by the compounds formed in Examples 12 and 13 then the corresponding product is obtained.

15 EXAMPLE 394-(3-(3-(2-QUINOLINYLMETHYLOXY) PHENYL) PROPYL) PHENOL

A solution of 4-(3-(3-(2-quinolinylmethyloxy)phenyl)-1-oxo-2-propen-1-yl)phenol (0.008 mol) in ethyl acetate (150 ml) is
20 shaken under 50 psi of hydrogen gas in the presence of 10% palladium on carbon catalyst (1.0 g). The reaction mixture is filtered through a celite pad and evaporated to give 4-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)phenol.

25 EXAMPLE 40

When 4-(3-(3-(2-quinolinylmethyloxy)phenyl)-1-oxo-2-propen-1-yl)phenol of Example 39 is replaced by the products prepared by Example 38, then the corresponding phenol is
30 prepared.

EXAMPLE 415-(3-CHLOROPROPYL)TETRAZOLE

5 A mixture of 3.5 g of 4-chlorobutyronitrile, 2.3 g of sodium azide and 1.9 g of ammonium chloride in 50 ml of dimethylformamide is stirred at 140°C for 20 hours. The reaction mixture is poured onto ice, basified with 1N sodium hydroxide and extracted twice with ethyl acetate. The
10 aqueous fraction is acidified with acetic acid and extracted with ethylacetate. Evaporation of the ethyl acetate gives 5-(3-chloropropyl)tetrazole which is used directly in the next step.

15

EXAMPLE 42

When 4-chlorobutyronitrile of Example 41 above is replaced by the nitriles of Table X below then the corresponding tetrazole product is obtained.

20

TABLE X

	chloroacetonitrile
	bromoacetonitrile
	3-chloropropionitrile
25	4-chlorobutyronitrile
	5-chloropentanitrile
	6-chlorohexanitrile
	2-chloropropionitrile
	2-methyl-3-chloropropionitrile
30	2-chlorobutyronitrile
	3-chlorobutyronitrile
	4-methyl-5-chloropentanitrile
	2-methyl-3-chloropropionitrile
	3-benzyl-4-chlorobutyronitrile
35	3-carbethoxymethyl-4-chlorobutyronitrile
	3-methoxymethyl-4-chlorobutyronitrile

- 2,3-dimethyl-4-chloropentanitrile
3,3-dimethyl-4-chloropentanitrile
spiro-(3,3-cyclopropane)-4-chlorobutyronitrile
1-chloromethyl-2-cyanomethylcyclobutane
5 1-chloromethyl-2-cyanomethylcyclohexane
3-cyclopropylmethyl-4-chlorobutyronitrile
3-dimethylaminomethyl-4-chlorobutyronitrile
3-methylene-4-chlorobutyronitrile
3-propylidene-4-chlorobutyronitrile

10

EXAMPLE 435-(3-(4-(3-(3-(2-QUINOLINYL METHYLOXY) PHENYL) PROPYL)-
PHENOXY) PROPYL) TETRAZOLE

- A mixture of (0.014 mol) 4-(3-(3-(3-(2-quinolinylmethyl-
15 oxy)benzyloxy)phenyl)propyl)phenol (0.14 mol) 5-(3-chloro-
propyl)tetrazole and 2 g (0.036 mol) KOH in 5 ml water and 50
ml ethanol is heated over a steam bath for a period of 3
hours. Reaction mixture is concentrated to dryness and
slurried into water and extracted with methylene chloride.
20 The methylene chloride extract is washed with water, dried
over MgSO₄ and concentrated under reduced pressure to obtain
solid which is passed through a silica gel column using
hexane/ethyl acetate as eluent. Evaporation of eluent gives
5-(3-(4-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)phenoxy)-
25 propyl)tetrazole.

EXAMPLE 44

- When 4-(3-(3-(3-(2-quinolinylmethyloxy)phenyl)propyl)-
30 phenol of Example 40 is replaced by the compounds prepared by
Examples 39 and 40 and 5-(3-chloropropyl)tetrazole is
replaced by the compounds prepared by Example 42, then the
corresponding product is obtained. A representative list of
compounds so prepared is shown below in Table XI.

TABLE XI

5	5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-methyl)tetrazole
	5-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-methyl)tetrazole
	5-(3-(4-(2-quinolinylmethyloxy)phenethyl)phenoxy-methyl)tetrazole
10	5-(2-(3-(2-quinolinylmethyloxy)phenethyl)phenoxy-methyl)tetrazole
	5-(4-(3-(2-quinolinylmethyloxy)phenethyl)-phenoxy-methyl)tetrazole
15	5-(2-(3-(3-(2-quinolinylmethyloxy)phenethyl)-phenoxy)propyl)tetrazole
	5-(2-(3-(4-(2-quinolinylmethyloxy)phenethyl)-phenoxy)ethyl)tetrazole
	5-(4-(2-(4-(3-quinolinylmethyloxy)phenethyl)-phenoxy)butyl)tetrazole

20

EXAMPLE 453-(4-(2-QUINOLINYL METHYLOXY) BENZYL) BENZYL ALCOHOL

Methyl 3-(4-(2-quinolinylmethyloxy)benzyl)benzoate (.002 mol) in tetrahydrofuran (50 ml) is added dropwise to a
 25 tetrahydrofuran (50 ml) suspension of lithium aluminium hydride (.004 mol). After consumption of the ester, the remaining lithium aluminum hydride is quenched by the addition of water and filtration to remove the resulting salts. Evaporation of the solvent gives 3-(4-(2-
 30 quinolinylmethyloxy)benzyl)benzyl alcohol.

EXAMPLE 465 3-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZYL ALCOHOL
MESYLATE

To methanesulfonyl chloride (0.002 mol) and triethylamine (0.002 mol) in dichloromethane (40 ml) at 0°C is added 3-(4-(2-quinolinylmethyloxy)benzyl)benzyl alcohol (0.0018 mol) in dichloromethane (40 ml) dropwise. After 24 hours, the
10 reaction mixture is washed with water, dried and evaporated to give 3-(4-(2-quinolinylmethyloxy)benzyl)benzyl alcohol mesylate.

EXAMPLE 4715 3-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) PHENYLACETONITRILE

3-(4-(2-Quinolinylmethyloxy)benzyl)benzyl alcohol mesylate (0.0018 mol) with sodium cyanide (0.0036 mol) in dimethylsulfoxide (10 ml) is stirred at ambient temperature. After the consumption of sulfate, the reaction is diluted
20 with water and extracted with ethyl acetate. The organic extracts are dried and evaporated to give 3-(4-(2-quinolinylmethyloxy)benzyl)phenylacetonitrile.

EXAMPLE 4825 5-(3-(4-(2-QUINOLINYLMETHYLOXY) BENZYL) BENZYL) TETRAZOLE

Sodium azide (0.0054 mol), ammonium chloride (0.0054 mol) 3-(4-(2-quinolinylmethyloxy)benzyl)phenylacetonitrile in dimethylformamide (5 ml) are heated at 110°C - 115°C for 24 hours. The product is isolated by pouring the reaction
30 mixture into 10% sodium hydroxide solution, washing with ethyl acetate, and inducing the crystallization by acidification with aqueous hydrogen chloride. This results in 5-(3-(4-(2-quinolinylmethyloxy)benzyl)benzyl)tetrazole.

The methods described above are used to prepare the following compounds of this invention.

- 5 5-[3-Methoxy-4-(3-(2-Quinolinylmethoxy)phenethyl)phenyl]-
tetrazole (M.P. 151-154°C)
CALC: C, 67.84; H, 5.56; N, 15.20
FOUND: C, 68.02; H, 5.62; N, 14.75
- 10 2-[4-(2-Quinolinylmethoxy)phenethyl]phenyl acetic acid
(M.P. 174-176°C)
CALC: C, 77.69; H, 5.89; N, 3.48
FOUND: C, 77.94; H, 6.11; N, 3.41
- 15 2-[4-(2-Quinolinylmethoxy)benzyl]phenyl acetic acid
(M.P. 183-186°C)
CALC: C, 77.40; H, 5.58; N, 3.61
FOUND: C, 77.19; H, 5.84; N, 3.56
- 20 5-[3-(4-(2-Quinolinylmethoxy)phenylpropan-2-yl)phenyl]-
tetrazole (M.P. 170-173°C)
CALC: C, 73.30; H, 5.56; N, 16.44
FOUND: C, 73.05; H, 5.85; N, 16.16
- 25 5-[3-(3-(2-Quinolinylmethoxy)phenethyl)benzyl]tetrazole
(M.P. 53-55°C)
CALC: C, 72.53; H, 5.62; N, 16.26
FOUND: C, 73.08; H, 5.68; N, 15.40
- 30 5-[3-(3-(2-Quinolinylmethoxy)phenylpropan-2-yl)phenyl]-
tetrazole (M.P. 83-86°C)
CALC: C, 70.40; H, 5.78; N, 15.77
FOUND: C, 70.81; H, 5.85; N, 15.45
- 35 5-[4-(4-(2-Quinolinylmethoxy)benzyl)phenyl]tetrazole
(M.P. 206-209°C)
CALC: C, 73.27; H, 4.87; N, 17.80
FOUND: C, 72.86; H, 4.97; N, 17.64

5-[3-(4-(2-Quinolinylmethoxy)benzyl)phenyl]tetrazole
(M.P. 186-189°C)

CALC: C, 66.42; H, 5.45; N, 16.13

5 FOUND: C, 66.27; H, 5.09; N, 16.09

5-[3-(3-(2-Quinolinylmethoxy)phenethyl)phenyl]tetrazole
(M.P. 126-129°C)

CALC: C, 69.11, H, 5.57; N, 16.12

10 FOUND: C, 69.27; H, 5.54; N, 16.43

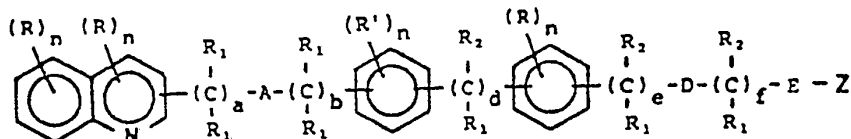
5-[3-(4-(2-Quinolinylmethoxy)phenethyl)phenyl]tetrazole
(M.P. 165-168°C)

CALC: C, 72.09; H, 5.32; N, 16.81

15 FOUND: C, 72.44; H, 5.64; N, 16.70

WE CLAIM:

1. A compound of the formula



5 where:

A is O or S;

D is O, S, NR₁, $\overset{R_1}{\underset{R_2}{\text{C}}} = \text{C}-$ or a chemical bond

10 E is a chemical bond or $\overset{R_1}{\underset{R_2}{\text{C}}} = \text{C}-$;

a is 0-2;

b is 0-1;

d is 1-5;

e is 0-4;

15 f is 0-5;

n is 0-2;

R is independently hydrogen, alkyl, hydroxy, alkoxy, carboxy, carbalkoxy, halo, nitro, haloalkyl, cyano or acyl;

20 R' is independently hydrogen, alkyl, hydroxy, alkoxy, halo or haloalkyl;

R₁ is independently hydrogen, alkyl or aralkyl;

R₂ is $-(\text{CH}_2)_x - \text{X}$;

x is 0-3;

25 X is hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, hydroxy, alkoxy, aralkoxy, amino, mono- and di-alkylamino, aralkylamino, acylamino, carbamyl, carboxy, carbalkoxy, tetrazolyl or acylsulfonamido;

vicinal R₂ groups together may be $-(\text{CH}_2)_y-$, where y is 1-4, thus forming a 3-6 membered ring;

30 geminal R₁ and R₂ groups may together form a spiro substituent, $-(\text{CH}_2)_z-$, where z is 2 to 5;

geminal R₁ or R₁ and R₂ groups may together form an alkylidenyl substituent, $=\text{CHR}_1$;

Z is $-\text{COOR}_1$, CN , $-\overset{\text{O}}{\text{C}}\text{NHSO}_2\text{R}_3$, $-\overset{\text{O}}{\text{C}}\text{N}(\text{R}_1)_2$, $-\text{OR}_1$, tetrazolyl or substituted tetrazolyl where the substituent may be alkyl, carboxyalkyl or carbalkoxyalkyl;

5 R_3 is hydrogen, alkyl, haloalkyl, phenyl or benzyl; and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 where:

A is O or S;

10 n is 0-1;

a + b is 1;

e + f is 0-5;

R and R' are hydrogen, alkyl or alkoxy;

R_1 is hydrogen or alkyl;

15 R_2 is $-(\text{CH}_2)_x - \text{X}$;

x is 0-3;

X is hydrogen or alkyl; and

Z is $-\text{COOR}_1$, $-\text{CN}$, $-\overset{\text{O}}{\text{C}}\text{NHSO}_2\text{R}_3$, $-\overset{\text{O}}{\text{C}}\text{N}(\text{R}_1)_2$ or tetrazolyl.

20 3. A compound according to claim 2 where:

A is O;

n is 0;

d is 1-3; and

Z is $-\text{COOR}_1$, $-\text{CN}$ or tetrazolyl.

25 4. A compound according to claim 3 where:

a is 1;

b is 0; and

d is 1.

30 5. A compound according to claim 3 where:

a is 1;

b is 0; and

d is 2.

35 6. A compound according to claim 3 where:

a is 1;

b is 0; and

d is 3.

7. A compound according to claim 3 where:

5 D is 0; and

E is a chemical bond.

8. A compound according to claim 3 where:

D is S; and

10 E is a chemical bond.

9. A compound according to claim 3 where:

e + f is 0;

D is a chemical bond; and

15 E is a chemical bond.

10. A compound according to claim 3 where:

e + f is 1-5;

D is a chemical bond; and

20 E is a chemical bond.

11. A compound according to claim 4 which is
5-(3-(3-(2-quinolinylmethyloxy)benzyl)phenyl)-
tetrazole.

25 12. A compound according to claim 5 which is
5-(4-(4-(2-quinolinylmethyloxy)phenethyl)phenyl)-
tetrazole.

13. A compound according to claim 5 which is
30 5-(4-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-
tetrazole.

14. A compound according to claim 4 which is
5-(3-methoxy-4-(3-(2-quinolinylmethyloxy)benzyl)-
35 phenyl)tetrazole.

15. A compound according to claim 4 which is
5-(4-methoxy-3-(3-(2-quinolinylmethyloxy)benzyl)-
phenyl)tetrazole.
- 5 16. A compound according to claim 4 which is
5-(4-(4-(2-quinolinylmethyloxy)benzyl)phenyl)-
tetrazole.
- 10 17. A compound according to claim 10 which is
5-(4-(4-(2-quinolinylmethyloxy)benzyl)benzyl)-
tetrazole.
- 15 18. A compound according to claim 10 which is
5-(4-(3-(4-(2-quinolinylmethyloxy)benzyl)phenyl)-
3-methylbutyl)tetrazole.
19. A compound according to claim 5 which is
5-(3-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-
tetrazole.
- 20 20. A compound according to claim 5 which is
5-(2-(3-(2-quinolinylmethyloxy)phenethyl)phenyl)-
tetrazole.
- 25 21. A method for the treatment of hypersensitive ailments
in humans and mammals comprising administering thereto
an effective amount of a compound of the formula
according to claim 1.
- 30 22. A pharmaceutical composition wherein the active
ingredient is a compound according to claim 1 in
admixture with a pharmaceutical carrier

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US88/03895

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC IPC(4): C07D 215/12; C07D 215/14; C07D 215/18; C07D 215/20; C07D 401/10; A61K 31/41; A61K 31/47; U.S.C1.: 546/168; 546/170; 546/171; See Attachment sheet 1.		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
U.S.	546/16; 546/168; 546/170; 546/171; 546/172; 546/176; 546/180; 546/101; 514/311; 514/314	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
CAS ON LINE		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	U.S., A, 4,282,230 (HOEHN) published 04 August 1981. See entire document.	
A	U.S., A, 4,661,499 (YOUNG) published 28 April 1987. See entire document.	
P,Y	U.S., A, 4,769,461 (MUSSER) published 06 September 1988. See entire document.	1-10 21 & 22
Y	EP, A, 0,206,751 (YOUNG) published 30 December 1986.	1-22
<p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
06 FEBRUARY 1989	22 MAR 1989	
International Searching Authority	Signature of Authorized Officer	
ISA/US	DAVID SPRINGER	

PCT/US88/03895
Attachment sheet 1

I. CLASSIFICATION OF SUBJECT MATTER (CONTINUED)

U.S.Cl.: 546/172; 546/176; 546/180; 546/16; 546/101; 514/311; 514/314